MEDICIS

The Dermatology Company®

December 20, 2005

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Comments Relating to Dockets No. 2005D-0340

Dear Sir or Madam:

Please note that the comments addressed in this letter were submitted in electronic form on December 19, 2005, at http://www.fda.gov/dockets/ecomments. In order to meet the 4000 character limit in the electronic submission, our comments were submitted in four parts and assigned Temporary Comment Numbers 44407 through 44410. The comments in this letter, however, reflect the comments submitted electronically as one complete package.

I am writing to provide comments on Docket No. 2005D-0340 "Draft Guidance for Industry on Acne Vulgaris: Developing Drugs for Treatment; Availability".

Medicis Pharmaceutical Company opposes the use of the Investigator Global Assessment (IGA), dichotomized or not, as a measure of efficacy in acne vulgaris. Rather Medicis believes that the use of lesion counts as proposed in the Draft Guidance should be the sole and primary clinical endpoint for determining efficacy.

The Division is aware of the numerous clinical trials in acne vulgaris that have used the IGA conducted by this Sponsor and others. We have the following issues with the Draft Guidance and the proposed use of the IGA that make implementation of the Draft Guidance impossible.

1. The Draft Guidance suggests that each company should validate its IGA before implementation.

This proposal creates a Catch-22. In the Draft Guidance the IGA is required, but it must be validated first. If the IGA cannot be validated, then a clinical study cannot proceed. Thus, there should really be at least one prior successful validation either by the agency or by academia before any requirement for an IGA is instituted. We are not aware of any products approved under the criteria outlined in the Draft Guidance. Generally, a company or academic organization will develop and validate an efficacy grading scale prior to its use in a pivotal study. This scale is then placed either in the public domain through validation by academia or through approval of a drug product by the company concerned. The agency

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THEN proposes that this scale should be adopted uniformly for any subsequent products looking at this indication. The draft guidance is thus backwards and creates a circumstance where it is theoretically possible that NO scale can be validated necessitating the withdrawal of the guidance after multiple attempts or fruitless research.

2. The sensitivity of the IGA to changes in non-inflammatory lesions is inappropriately low.

Validation generally involves two substantially different tests that must be performed. The first is a correlation between the results of the efficacy scale and some other well-accepted scale. [The second is inter- and intra-observer validation; *see* no. 9.] This would be an assessment of sensitivity and specificity of the proposed scale against some well-accepted methodology. Previously submitted analysis of randomized controlled clinical trial data from several NDAs establish that the scale is reasonably effective in the tested populations in duplicating the sensitivity and specificity of changes in inflammatory lesion count but is NOT sensitive to improvements in non-inflammatory lesion count. At the November 4-5, 2003 Advisory Panel Meeting the Division indicated that inflammatory lesions had four times the impact on the IGA as did non-inflammatory lesions. Clinicians testified at the Advisory Panel that the IGA is NOT a good measure of efficacy. Thus raising doubts that the proposed scale could be validated.

3. The sensitivity and specificity of the IGA against changes in inflammatory lesion counts has not been performed.

At the Advisory Panel Meeting, Dr. Leyden described retrospective validation against inflammatory lesions as inappropriate. He commented that patients with marked clinical improvement in lesion counts may not be 'clear or almost clear', the dichotomized IGA. This would mean that the sensitivity to detect clinical improvement with the dichotomized IGA is not adequate. Dr. Leyden's proposal was that 2-grade improvement in addition to 'clear or almost clear' be used if an IGA is used at all. The Draft Guidance only partially includes this recommendation. If an IGA is used it should be dichotomized based on "clear, almost clear or 2-grades of improvement. While this accepts the position of Dr. Leyden, the acceptance begs the question of whether any of the proposed IGA success criteria is any better at measuring meaningful clinical improvement.

4. Validation should be prospective.

No prospective validation of the IGA scale against an objective measurement of clinical improvement has been performed.

5. The IGA scale is unnecessary.

The presumption underlying the development of the IGA scale is that there is a problem with a pre-existing measurement or instrument for determining efficacy of a drug product. The pre-existing measurement of efficacy is lesion counting. The objections identified with

lesion counting are that it is cumbersome and may not represent clinical improvement. *Since it is acne lesions that are the subject of the treatment, direct counts are the most relevant measure of improvement.* Thus the objections to use of lesion counts are not an acceptable justification for mandating development of a new untested and untried scale.

6. Well-performing outliers can confound the IGA Scale.

Based on existing data available to the Division, the IGA scale is designed to indicate efficacy based on a small proportion of patients successfully achieving the endpoint of 'clear or almost clear'. This may cause the IGA scale to be inaccurate if a small number of patients were to achieve 'success' through investigative error or unexpected improvement. If a few patients are incorrectly judged a 'success' are in the active arm, a false positive result may occur; if the few successful patients are in the placebo arm, then a 'false negative' result may occur. Stated differently, because most patients do not achieve a successful endpoint and therefore do not count towards efficacy, the scale is subject to a high rate of false positive and false negative observations.

7. The IGA scale cannot differentiate products that are effective against one or the other type of lesion.

The point was made at the Advisory Panel that products that are intended for the treatment of only one lesion type, either non-inflammatory lesions or inflammatory lesions, should be approved. The guidance provides for approvals for a single lesion type and requires the use of the IGA Scale even though the scale has been shown to be heavily weighted to improvements in inflammatory lesions.

8. The IGA scale is insensitive to detecting differences between two products that may act on the same lesion type.

The development of combination acne products requires the comparison of the combination against each of its components. Comparisons of the combination (containing ingredients improving inflammatory and non-inflammatory lesions) to the product containing only the anti-inflammatory lesion component should show the superiority of the combination in improving non-inflammatory lesions. However, the IGA is not adequately sensitive to detect clinically meaningful changes in non-inflammatory lesions, and therefore the IGA will consistently fail to support the efficacy of the combination product when efficacy exists. Because the IGA is heavily weighted in favor of inflammatory lesions the above comparison will both show similar IGA improvements even though the single component provides little or no improvement in non-inflammatory lesions.

9. Use of the IGA scale imposes an unreasonably high degree of certainty upon success since the scale is in addition to lesion counting.

Since lesion counting is still used, and one must meet statistically significant success on both lesion counts and the IGA, the Division is increasing the difficulty of identifying success above the statutory and regulatory level of two adequate and well-controlled trials. There should be a corresponding upward modification of the p value to account for requiring the product to meet two independent tests of success. If the two scales are dependent upon each other, of course, a new scale is not required.

10. Inter- and intra-observer validation has not been performed.

There is no evidence that the scale CAN be validated to inter-observer or intra-observer accuracy. These forms of validation have never been done in the retrospective analyses of Wilkins and Alosh. Before implementation, identification as to whether any version (including scales with photographs) of the IGA scale can be implemented alike by different observers. Since the scale also requires future assessments, we need to know if the same patient with the same features would be graded the same by the same observer at two different time points. This may be difficult to ascertain unless good photographic standards can be developed. Again, both validations should be performed on some permutation of the IGA scale prospectively BEFORE a requirement is imposed to demonstrate that at least one permutation of the scale may be possible.

11. There is no perceived need for a new scale.

The draft guidance does not identify any scientific or medical rationale for supplementation or replacement of the lesion counting scale.

12. The Draft Guidance is not specific as to whether the IGA scale is a visual only scale.

Physical palpation and physical examination of the patient is needed to identify lesion types and lesion number. Completing the IGA without palpation assures inaccurate use of the IGA grade descriptions. The IGA requires identification of lesion types and number. In addition, photographic scales do not permit the standardization of lesion identification and counting because palpation is not possible.

13. The IGA scale is inaccurate and insensitive in skin of color.

The IGA will be confounded in dark-skinned patients in two ways: a) post-inflammatory pigmentary changes (PIH) can be confused with ongoing disease although the underlying lesions have successfully resolved on test therapy; and b) lesions cannot be readily detected in patients with Fitzpatrick Skin Type VI because the erythema of inflammatory lesions may not be evident visually. In any event, validation of the successful use of any such IGA scale

in this patient subset should be accomplished before any form of such a scale is made mandatory.

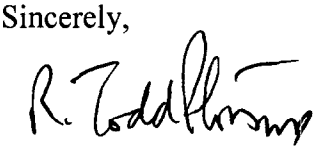
14. The IGA scale is confounded by baseline severity

Ideally, an efficacy scale should provide near linear grades of improvement so that improvement from lower or worse disease is measured equally to improvements from milder disease. The dichotomous nature of the scale does not allow for accurate measurements of clinical improvement of severe disease as compared to measurement of improvements in milder disease. In a presentation by Dr. Alosh at the Advisory Panel it was stated that severe patients had a much lower chance of achieving success than moderate or mild patients. First, it is unclear whether requiring 2-grades of improvement as the definition of success for mild patients is helpful, since we do not know if improvement from severe to mild is similar to improvement from moderate to almost clear or, similarly, from mild to clear. This requires prospective assessment with a validated scale and use of an agent known to be effective as a test agent. If the IGA scale, as is believed, is non-linear, then use of 'clear or almost clear' or '2-grades of improvement' may not correct the bias introduced by overpopulating a study with moderate or mild patients (as compared to a randomly picked population). The ability to overpopulate a study with one type of disease severity and, thereby affect rate of success means that the scale is susceptible to gaming by investigators or study sponsors. For instance, an investigator can acquire a reputation for selectively including more mild patients and thus attract more sponsor study contracts.

15. The Agency's expressed view that acne is a cosmetic disease is not supported by the clinical or patient community.

One rationale for the scale is that if a patient is not visually improved, then the drug product is ineffective because the disease is cosmetic only. However, even non-inflammatory lesions can result much later in pitting scars or keloid formation. Thus, improvement in lesion counts provides a clinical benefit that does not correspond to what might be missed in a visual IGA examination.

Sincerely,



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